



**EXHIBIT D  
ISSUED CLAIMS**

**U.S. PATENT NO. 5,863,538 (3999.000700; UTSD:452)**

1. (Thrice Amended) In combination,
  - (a) a first pharmaceutical composition comprising a first antibody which is a bispecific antibody that binds to both an activating antigen on the cell surface of a leukocyte cell and a tumor antigen on the cell surface of tumor cells of a vascularized solid tumor, the bispecific antibody being effective to induce the expression of a cytokine by a leukocyte; and
  - (b) a second pharmaceutical composition comprising a second antibody or antigen binding fragment thereof operatively linked to a selected therapeutic or diagnostic agent, the second antibody binding to a cytokine-inducible endothelial cell antigen that is induced on the surface of intratumoral blood vessels of a vascularized tumor by said cytokine.
2. (Thrice Amended) The combination of claim 1, wherein the first antibody binds to the leukocyte cell surface activating antigen CD2, CD3, CD14, CD16, FcR for IgE, CD28 or the T-cell receptor antigen.
3. (Thrice Amended) The combination of claim 2, wherein the first antibody binds to CD14, and induces the expression of the cytokine IL-1 or TNF- $\alpha$  by monocyte/macrophage cells.
4. (Twice Amended) The combination of claim 3, wherein the second antibody binds to the cytokine-inducible antigen, ELAM-1.
5. (Thrice Amended) The combination of claim 2, wherein the first antibody binds to CD28, and induces the expression of the cytokine IFN- $\gamma$  by T-cells.
6. (Twice Amended) The combination of claim 5, wherein the second antibody binds to a cytokine-inducible MHC Class II antigen.
7. The combination of claim 6, further including a third pharmaceutical composition comprising cyclosporin A.

8. (Amended) The combination of claim 2, wherein the first antibody binds to CD14 or CD28 and to a tumor antigen.

9. (Twice Amended) The combination of claim 1, further including a third pharmaceutical composition comprising an anti-tumor cell immunotoxin in which an anti-tumor cell antibody or antigen binding fragment thereof is operatively attached to a selected therapeutic agent.

10. (Thrice Amended) The combination of claim 9, wherein the anti-tumor cell immunotoxin binds to a tumor antigen selected from the group consisting of p185<sup>HER2</sup>, milk mucin core protein, TAG-72, Lewis a, carcinoembryonic antigen (CEA), a high Mr melanoma antigen and an ovarian tumor-associated antigen.

11. (Four Times Amended) The combination of claim 1, wherein the first antibody binds to a tumor antigen selected from the group consisting of p185<sup>HER2</sup>, milk mucin core protein, TAG-72, Lewis a, carcinoembryonic antigen (CEA), a high Mr melanoma antigen and an ovarian tumor-associated antigen.

12. (Twice Amended) The combination of claim 1, wherein the second antibody or fragment is operatively linked to a selected therapeutic agent.

13. The combination of claim 12, wherein the selected therapeutic agent is an anticellular agent capable of killing or suppressing the growth or cell division of endothelial cells.

14. The combination of claim 13, wherein the anticellular agent is a chemotherapeutic agent, a radioisotope or a cytotoxin.

15. The combination of claim 13, wherein the anticellular agent is a steroid, an antimetabolite, an anthracycline, a vinca alkaloid, an antibiotic, an alkylating agent or an epipodophyllotoxin.

16. The combination of claim 13, wherein the anticellular agent comprises a plant-, fungus- or bacteria-derived toxin.

17. The combination of claim 16, wherein the toxin comprises an A chain toxin, a ribosome inactivating protein,  $\alpha$ -sarcin, aspergillin, restrictocin, a ribonuclease, diphtheria toxin or *Pseudomonas* exotoxin.

18. The combination of claim 17, wherein the toxin comprises ricin A chain.
19. The combination of claim 18, wherein the toxin comprises deglycosylated ricin A chain.
20. (Twice Amended) The combination of claim 1, wherein the first antibody binds to an activating antigen on the cell surface of a leukocyte cell and induces the cell to produce the cytokine IL-1, IL-4, TNF- $\alpha$ , TNF- $\beta$  or IFN- $\gamma$ .
21. (Twice Amended) The combination of claim 1, wherein the first antibody binds to an activating antigen on the cell surface of a monocyte, macrophage, mast cell, helper T cell, CD8-positive T-cell or NK cell.
22. (Twice Amended) The combination of claim 1, wherein the first antibody binds to a cell surface activation antigen of mature effector cells selected from the group consisting of CD5, CD8, CD11/CD18, CD15, CD32, CD44, CD45 and CD64; or to a leukocyte activation antigen selected from the group consisting of CD25, CD30, CD54 and CD71.
23. The combination of claim 1, wherein the second antibody binds to ELAM-1, VCAM-1, ICAM-1, a ligand reactive with LAM-1, endoglin or an MHC Class II antigen that is induced on the surface of intratumoral blood vessels of a vascularized tumor by said cytokine.